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Wavelength tuneable led light source

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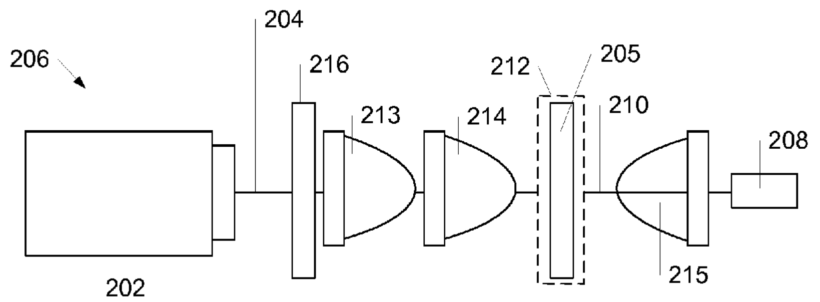


Fig. 2

(57) Abstract: Disclosed herein is an illumination system (200) for spectrally tuning in fluorescence imaging applications such as endoscopic applications in a body cavity comprising bodily fluids or microscopic applications.

WO 2017/137350 A1

Wavelength tuneable LED light source

The invention relates to an easy and inexpensive illumination source for spectral tuning of light sources in fluorescence imaging systems.

Background

Spectral tuning of light sources in fluorescence imaging is a very convenient method of achieving the optimal contrast by exciting the proper fluorophore. There are a variety of methods suitable for this purpose each providing either ease of operation, high scan speed or high bandwidth. It is customary for professionals in the field of fluorescence microscopy to make use of spectral tuning to excite different fluorophores in the sample to contrast different organelles or morphological changes in e.g., biopsies.

The most common method being employed in fluorescence microscopy is the use of different colour filters typically mounted in a filter cube. Previously, the preferred light source for use in such fluorescence microscopes would be a xenon- or mercury discharge lamp. However, due to the massive development in solid state light sources like the LEDs (light emitting diodes) for lighting, projection display and flat screen TVs, the output power of LEDs have now reached a level where they can compete with the old-fashioned discharge lamps. Consequently, a number of the leading suppliers of photonic components are now offering LED based light source for microscopy and machine vision applications.

Also the field of endoscopy has benefitted from the current development in solid light sources and more and more suppliers of endoscopic devices are offering LED based light sources for the endoscope optics.

The common denominator of all the LED based light source is that the wavelength selection is done by changing a filter having fixed colour (i.e. a fixed wavelength). Depending on the requirements of the use of the lamp, this filter may be an absorption filter or an interference filter.

About 15 years ago a more elaborate method found its way into the field of fluorescence microscopy illumination. This technique was based on the use of a so-called Acousto Optic Tuneable Filter (AOTF), a device based on creating a dynamic grating inside a dielectric material by means of ultrasound. Changing the frequency of the ultrasonic transducer into the dielectric material changes the spatial frequency of the standing wave pattern generated by the ultrasonic pressure wave. The function of the AOTF is similar to that of a monochromator using a mechanically driven diffraction grating. The AOTF is, however, very compact compared to that of a monochromator and is the preferred method for rapid change of excitation wavelength in fluorescence microscopy if cost is not an issue.

A similar tuneable light source used in high-end fluorescence microscopy and spectroscopy (hyper- and multi spectral imaging) is the variable liquid crystal tuneable filter (LCTF). This device makes use of the electrically controlled birefringence of liquid crystal modulator. Although the tuning properties of the LCTF and AOTF are comparable, the speed of the two devices differs significantly. Due to the basic physical properties of liquid crystal light modulators (twisted nematic type), a tuning speed on the order of milliseconds versus microseconds for that of an AOTF can be achieved. In either cases these tuneable light source are expensive and targeted at users with a need for spectral control over the entire visible spectrum.

In recent years a new type of light sources have emerged know as super-continuum light sources. This kind of light source is a white light source. The white light (super-continuum) is generated by exciting optical non-linear effects in a photonic crystal fibre with pico- or femtosecond laser. As the core size of the optical fibre is around 40 microns, the light emitted from the light source will be partially spatial coherent (laser like). To spectrally tune this light source the aforementioned acousto-optic tuneable filter (AOTF) is used to select the appropriate wavelength form the super-continuum light source. It is apparent that this light source is a high-end product intended for challenging applications in the field of fluorescence microscopy and spectral imaging in biomedicine.

Description of the invention

The light source disclosed in this patent application, is aiming at light sources for use in fluorescence assisted imaging such as e.g. cystoscopy for photodynamic diagnosis and autofluorescence imaging where only a selected spectral tuning range is required.

Disclosed herein is an illumination system for fluorescence imaging applications. The fluorescence imaging applications may be endoscopic applications in a body cavity comprising bodily fluids or microscopic applications.

The illumination system comprises:

- a light emitting diode (LED) emitting substantially monochromatic LED light, wherein the LED is the single light source in the illumination system, and wherein the LED light emitted from the LED:
    - has an initial half width full maximum (FWHM),

    - has an initial central wavelength between 500 and 900 nm,
- an optical bandpass filter adapted to reduce the initial FWHM, whereby LED light with a reduced FWHM is obtained;
- means for tilting the optical bandpass filter thereby tuning the initial central wavelength of the LED light such that tuned LED light with a blue-shifted central wavelength is obtained;
- an optical transmission path adapted to guide the tuned LED light to a region of interest being e.g. an endoscopic region of examination or a microscopic imaging plane;
- an optical collection path adapted to guide light emitted and/or reflected light from the region of interest;
- a band-rejection filter adapted to attenuate at least a part of the tuned LED wavelength for a viewer, and
- an additional filter adapted for blocking light below 500 nm, the additional filter being positioned before or after the bandpass filter.

Hereby is obtained that the wavelength of the excitation light can be tuned easily within a range of approximately 15-50 nm using inexpensive equipment. This is highly advantageous as e.g. autofluorescence inside a cavity in a patient studied with endoscopes or from human samples studied with fluorescence microscopy, will vary from patient to patient. The optimum excitation wavelength for one patient / sample giving the best contrast for that specific patient may not be the best wavelength for another patient / sample.

The autofluorescence inside the bladder e.g. varies from patient to patient, and tuning of the LED in the illumination system ensures that the optimal contrast between the different fluorescence colors can be obtain individually for each patient without changing any filters or using expensive equipment.

In one or more embodiments, the initial central wavelength is between 500 and 550 nm.

In one or more embodiments, the initial central wavelength is between 550 and 600 nm.

In one or more embodiments, the initial central wavelength is between 600 and 650 nm.

In one or more embodiments, the initial central wavelength is between 650 and 700 nm.

In one or more embodiments, the initial central wavelength is between 700 and 750 nm.

In one or more embodiments, the initial central wavelength is between 750 and 800 nm.

In one or more embodiments, the initial central wavelength is between 800 and 850 nm.

In one or more embodiments, the initial central wavelength is between 850 and 900 nm.

In one or more embodiments, the blue-shifted central wavelength is up to 50 nm lower than the initial central wavelength.

In one or more embodiments, the blue-shifted central wavelength is between 15-50 nm lower than the initial central wavelength.

In one or more embodiments, the optical bandpass filter is an interference filter.

In one or more embodiments, the additional filter is a cut-off filter.

In one or more embodiments, the illumination system further comprises a first hybrid aspheric lens and a second hybrid aspheric lens both positioned between the bandpass filter and the LED.

In one or more embodiments, the means for tilting the optical bandpass filter is a mechanical piezo or electronic adjustments means.

In one or more embodiments, the means for tilting the optical bandpass filter can tilt the optical bandpass filter around a first axis and/or a second axis, wherein both the first axis and the second axis extend through the middle of the bandpass filter along directions being perpendicular to the direction in which the LED light propagates, the second axis being perpendicular to the first axis.

In one or more embodiments, the optical transmission path and the optical collection path are fibres extending inside an endoscopic tube, the endoscopic tube having a proximal end where tuned LED light enters the optical transmission path, and light emitted and/or reflected light from the endoscopic region of examination exits by the optical collection path, and a distal end where tuned LED light exits the optical transmission path and light emitted and/or reflected light from the endoscopic region of examination is collected by the optical collection path.

In one or more embodiments, the fibres are multimode fibres.

In one or more embodiments, the band-rejection filter is adapted to attenuate the predefined wavelength by more than 10 dB, preferably by more than 20 dB, preferably by more than 30 dB, preferably by more than 40 dB, preferably by more than 50 dB, most preferably by more than 60 dB.

In one or more embodiments, a solid state imaging device is located at a distal end of the illumination system.

In one or more embodiments, the solid state imaging device is a CCD (charge-coupled device) camera.

In one or more embodiments, the solid state imaging device is a CMOS (complementary metal–oxide–semiconductor) camera.

In one or more embodiments, the illumination system includes a digital solution for a digital endoscope. In there, a camera, e.g. in the form of a camera chip, is located at the distal end of the illumination system. The camera comprises an integral colour filter, e.g. in the form of a so-called Bayer mosaic colour filter. This filter makes it possible for the camera to see light in three spectral regions – red, green and blue commonly referred to as RGB. This means that the image transmitted from the distal part of the illumination system subsequently can further be electronically processed to suppress excitation light from the light source and enhance the fluorescence image of tumours and healthy tissue.

In one or more embodiments, the integral colour filter acts as the band-rejection filter as it attenuates the tuned LED wavelength.

Disclosed herein is also an endoscope comprising an illumination system according to the above. The endoscope may be a digital endoscope. A solid state imaging device, such as e.g. a CCD or CMOS camera, may be located at a distal end of the endoscope.

Disclosed herein is also a method for tuning the wavelength of a light source for use in endoscopic photodynamic diagnostic in the cavity of a patient, the method comprising the steps of providing an illumination system according to the above and tilting the bandpass filter around a first and/or a second axis, thereby tuning the light from the LED towards shorter wavelengths, wherein both the first axis and the second axis extend through the middle of the bandpass filter along directions being perpendicular to the direction in which the LED light propagates, the second axis being perpendicular to the first axis.

In one or more embodiments, the tilting of the bandpass filter is done automatically based on an optimization for obtaining the most contrast in the fluorescence signal.

In one or more embodiment, the endoscope is made from a material which can be reused.

Disclosed herein is also a system comprising an illumination system according to the above, and a high intensity treatment light source adapted for photo induced denaturation of tumour tissue inside the bladder in connection with treatment of bladder tumours, wherein the high intensity treatment light source is a solid state light source emitting light at a wavelength between 800-1000 nm or between 350-500 nm.

Brief description of the drawings

Figure 1 schematically illustrates an illumination system according to the invention used in connection with endoscopic applications.

Figure 2 is a close-up of the LED light source system with a tiltable bandpass filter.

Figure 3 shows a tuning curve for spectrally tuning a bandpass filter.

Figure 4A schematically illustrates a bladder as an example of a cavity inside a patient

Figure 4B shows an image of the bladder before tuning the LED wavelength and 4C shows an image of the bladder after tuning the LED wavelength to obtain a maximum contrast signal for the viewer.

Figure 5 schematically illustrates an illumination system according to the invention in combination with a high intensity treatment light source adapted for photo induced denaturation of tumour tissue inside a patient’s cavity.

Figures 6a-c show in vitro results for diode laser treatment on chicken breast meat.

Figures 7a-e show in vivo results for diode laser treatment on a tumour in the bladder of a patient from the before treatment (figure 7a), during treatment (figure 7b), immediately after end treatment (figure 7c) and after end treatment (figures 7c-d).

Description of preferred embodiments

Disclosed herein is an illumination system for fluorescence imaging applications such as endoscopic applications in a body cavity comprising bodily fluids or microscopic applications. The illumination system 200 may be adapted for inducing fluorescence in exogenous or endogenous fluorophores for performing photodynamic diagnosis (PDD).

The illumination system is shown schematically in figure 1 for the application of endoscopic use. In general the illumination system 200 comprises a light source in the form of an LED 202 emitting substantially monochromatic LED light 204. The LED is the single light source in the illumination system 200, and the LED light has an initial half width full maximum (FWHM), and an initial central wavelength between 500 and 900 nm.

The LED light 204 typically have an emission spectrum with a FWHM of between 15 and 100 nm.

In one or more embodiments, the LED light have an emission spectrum with a FWHM of between 20 and 75 nm, or between 30 and 50 nm or between 35 and 45 nm.

In one or more embodiments, the predefined central wavelength of the LED may be between 500 and 550 nm, or between 550 and 600 nm, or between 600 and 650 nm, or between 650 and 700 nm, or between 700 and 750 nm, or between 750 and 800 nm, or between 800 and 850 nm, or between 850 and 900 nm.

In one or more embodiments, the predefined central wavelength of the LED may be between 500 and 505 nm, or between 505 and 510 nm, or between 510 and 515 nm, or between 515 and 520 nm, or between 520 and 530 nm, or approx. 525 nm, or between 525 and 530 nm, or between 530 and 535 nm, or between 535 and 540 nm, or between 540 and 545 nm, or between 545 and 550 nm, or between 550 and 555 nm, or between 555 and 560 nm, or between 560 and 565 nm, or between 565 and 570 nm, or between 570 and 575 nm, or between 575 and 580 nm, or between 580 and 585 nm, or between 585 and 590 nm, or between 590 and 595 nm, or between 595 and 600 nm.

The illumination system 200 also comprise an optical bandpass filter 205 adapted to reduce the initial FWHM, whereby LED light with a reduced FWHM is obtained.

When using an LED with a central wavelength between 500-550 nm, the FWHM of the unfiltered LED light is approx. 40 nm, whereas the spectrum of the LED light covers a span from 450 nm to 600 nm. In specific applications such as photodynamic diagnostics of bladder cancer (see further examples discussed later in this document), this is not desirable because the "blue" 450-500 nm range is unwanted due to stimulation of green fluorescence from urine. Likewise, the "red" 550-600 nm range will confound the native fluorescence of the tissue.

To narrow the emission spectrum of the LED light 204, the bandpass filter 205 is inserted in the optical path between the LED and an optical transmission path 208. Figure 2 shows a close up of the setup 206 around the bandpass filter 205 and the LED 204.

The bandpass filter 205 reduces the FWHM to approx. 25 nm thereby reducing the lower wavelength light that may induce fluorescence in e.g. urine and also reducing the longer wavelength light that may be allowed through the band-rejection filter, i.e. the filter maximizes the desired sensitized fluorescence from cancerous tissue as well as the native autofluorescence of the healthy tissue.

The illumination system also comprises means 212 for tilting the optical bandpass filter 205 thereby tuning the initial central wavelength of the LED light such that tuned LED light 208 with a blue-shifted central wavelength is obtained. In figure 2, the means for tilting the optical bandpass filter is illustrated as a box 212 around the filter 205.

The means for tilting the optical bandpass filter may tilt the optical bandpass filter around a first axis and/or a second axis, wherein both the first axis and the second axis extend through the middle of the bandpass filter along directions being perpendicular to the direction in which the LED light propagates. The second axis being perpendicular to the first axis.

Figure 3 shows a tuning curve for spectrally tuning the bandpass filter, where the spectral transmission curve of a bandpass filter is blue-shifted when the bandpass filter is tilted 10 or 20 degrees in the plane of incidence. By plane of incidence is meant the plane defined by the first and the second axis, i.e. the optical plane. Thus, the tilting of the bandpass filter is done with respect to the optical axis.

The means for tilting the optical bandpass filter may be purely mechanical mounts allowing for rotation about the plane of incidence or similar mechanical mounts driven by actuators based on either electromagnetic means or piezo-based devices.

In one or more embodiments, the means for tilting the optical bandpass filter is an opto-mechnical component like a gimbal mount allowing the filter to be tilted in the aforementioned manner. This component can either be operated manually or by means of electromagnetic actuators or piezo actuators.

In one or more embodiments, the optical bandpass filter is an interference filter.

In one or more embodiments, the blue-shifted central wavelength is up to 50 nm lower than the initial central wavelength.

In one or more embodiments, the blue-shifted central wavelength is up to 40 nm lower than the initial central wavelength.

In one or more embodiments, the blue-shifted central wavelength is up to 30 nm lower than the initial central wavelength.

In one or more embodiments, the blue-shifted central wavelength is up to 20 nm lower than the initial central wavelength.

In one or more embodiments, the blue-shifted central wavelength is between 15-50 nm lower than the initial central wavelength.

In one or more embodiments, the blue-shifted central wavelength is between 15-40 nm lower than the initial central wavelength.

In one or more embodiments, the blue-shifted central wavelength is between 15-30 nm lower than the initial central wavelength.

In one or more embodiments, the blue-shifted central wavelength is between 15-20 nm lower than the initial central wavelength.

The tilting of the bandpass filter may be done automatically based on an optimization for obtaining the most contrast in the fluorescence signal. The optimization will normally be an iterative process based on an algorithm included in a computer connected to the illumination system. The system will normally use region of interest (ROI) data from the imaging system to evaluate optimal contrast based on a look up table (LUT).

The illumination system may in one or more embodiments further comprises an additional filter 216 adapted for blocking light below a specific wavelength, the additional filter being positioned before or after the bandpass filter. In figure 2 the additional filter 216 is positioned before the bandpass filter 205. In connection with bladder cancer detection, a filter, which blocks light below 500 nm is normally used.

In one or more embodiments the additional filter 216 is a cut-off filter.

In one or more embodiments, the illumination system further comprises a first hybrid aspheric lens 213 and a second hybrid aspheric lens 214 both positioned between the bandpass filter 205 and the LED 202 .

A third hybrid aspheric lens 215 may also be found in the system being positioned between the bandpass filter 205 and the optical transmission path 208.

The first and second hybrid aspheric lenses 213, 214 may form a refractive-diffractive pair. Combined with the third hybrid aspheric lens 215, a condensate system is formed.

An optical transmission path 208 adapted to guide the tuned LED light 210 to either an endoscopic region of examination, e.g. the bladder, or to an optical illumination plane in a microscope is also part of the illumination system 200. An example of such is shown in figure 2 illustrated by the entrance to a fibre.

In one or more embodiments, a first fibre is connected to or part of the LED. The first fibre may be the optical transmission path 208. The fibre may further by extending through an endoscopic tube 226 as shown in figure 1 when an endoscope and the LED light source 202 are connected. The fibre may be a multimode fibre.

Light 218 emitted and/or reflected light from the region of interest, e.g. the endoscopic region of examination or the optical illumination plane in a microscope, is collected in an optical collection path 220 and guided to an electronic imaging device 222 allowing the practitioner or surgeon to observe the region of interest or the sample. A CCD camera may be used in this context.

An example of an optical collection path is a second fibre connected to or part of the LED. The second fibre may further by extending through an endoscopic tube 226 as shown in figure 1 when an endoscope and the LED light source 202 are connected. The second fibre may be a multimode fibre.

A coherent optical fibre bundle may also be used as the optical transmission path 208 and the optical collection path 220. The light illuminating the region of interest and the light reflected from this region is in this case normally separated by a mirror, e.g. a dichroic mirror.

The illumination system 200 may also comprise a band-rejection filter 224 adapted to attenuate at least a part of the tuned LED wavelength 208 for the viewer. In one or more embodiments, the band-rejection filter 224 attenuates the majority of the tuned LED wavelength 208 for the viewer.

The band-rejection filter 224 may be a narrow band rejection filter, such as a notch filter, preferably a Raman notch filter, also known as a rugate filter. Another example of a narrow band rejection filter that can be used is a Fabry-Perot etalon.

In the one or more embodiments of the invention, the rejection band of the band-rejection filter 224 comprises the tuned LED wavelength 208. Preferably the rejection band of the band-rejection filter is centred closed to the tuned central LED wavelength 208.

The band-rejection filter 224 may be designed such that it blocks wavelengths below around the central wavelength of the monochromatic tuned LED 210 and allows wavelengths above this wavelength to pass through.

In one or more embodiments, the illumination system includes a digital solution for a digital endoscope. In there, a camera, e.g. in the form of a camera chip, is located at the distal end of the illumination system. The camera comprises an integral colour filter, e.g. in the form of a so-called Bayer mosaic colour filter. This filter makes it possible for the camera to see light in three spectral regions – red, green and blue commonly referred to as RGB. This means that the image transmitted from the distal part of the illumination system subsequently can further be electronically processed to suppress excitation light from the light source and enhance the fluorescence image of tumours and healthy tissue.

In one or more embodiments, the integral colour filter acts as the band-rejection filter as it attenuates the tuned LED wavelength.

The band-rejection filter is preferably adapted to attenuate the tuned LED wavelength by more than 10 dB, preferably by more than 20 dB, preferably by more than 30 dB, preferably by more than 40 dB, preferably by more than 50 dB, most preferably by more than 60 dB.

Endoscopic applications

In one or more embodiments, the optical transmission path and the optical collection path are fibres extending inside an endoscopic tube, the endoscopic tube having:

- a proximal end where tuned LED light enters the optical transmission path, and light emitted and/or reflected light from the endoscopic region of examination exits by the optical collection path
- a distal end where tuned LED light exits the optical transmission path and light emitted and/or reflected light from the endoscopic region of examination is collected by the optical collection path.

In one or more embodiments, the endoscope further comprises biopsy extracting means adapted for extraction a biopsy sample from e.g. the bladder, wherein the biopsy extracting means extends into the patient’s bladder through an auxiliary channel in the endoscopic tube.

In one or more embodiment, the endoscope is a digital endoscope.

In a digital solution, a miniature CCD camera may be located at the distal end 228 of the endoscope 200 whereby the digital image formed in the CCD camera can be transmitted via an electrical connection to the proximal end, thereby eliminating the need for an optical relay system for transmitting images from the distal to the proximal end.

In one or more embodiments, the CCD camera comprises an integral colour filter, e.g. in the form of a so-called Bayer mosaic colour filter. This filter makes it possible for the camera to see light in three spectral regions – red, green and blue commonly referred to as RGB. This means that the image transmitted from the distal part of the illumination system subsequently can further be electronically processed to suppress excitation light from the light source and enhance the fluorescence image of tumours and healthy tissue.

In one or more embodiment, the endoscope is made from a material which can be reused.

The illumination system may e.g. be used for photodynamic diagnostic of bladder cancer. Figure 4A schematically illustrates a bladder 100 with three tumours 102, 104 inside the bladder wall and the urethra 106 leading into the bladder cavity 100.

In one or more embodiments, means for guiding the movement of the endoscopic tube when inserting the distal end 228 of the endoscopic tube 226 into the patient’s bladder 100 through the patient’s urethra 106 is also included in the illumination system.

A common problem encountered in endoscopic examination of bladders is that urine has a relatively strong absorption in the UV-blue region. Many commercial monochromatic light sources, used for photodynamic diagnosis or other methods for visualizing malignant tissue, emit light in the UV-blue region and thus cause strong green fluorescence in urine that confounds the sensitized fluorescence of the malignant tissue. As urine enters the bladder constantly during examination this problem cannot be avoided and prevents the use of photodynamic diagnosis for bladder cancer to be used in the outpatient department (OPD). Normally an endoscope utilizes two wavelength bands, one bright white light source used for illuminating the bladder with white light and a narrow band of light obtained by optically filtering the white light source for exciting the fluorophore of the photosensitizer. The physician locates the pre-cancerous tissue with the fluorescent light and switches to white light in order to remove the pre-cancerous tissue surgically. Thus, the physician has to switch between the two light sources during examination.

Another problem encountered in diagnostic methods based on fluorescent labeling and photodynamic diagnosis of pre-cancerous tissue in the bladder is photobleaching of the fluorophores used for labeling. Photobleaching is primarily caused by bright blue light sources used for illuminating the bladder. The consequence is that some precancerous tissues may remain undetected by the physician.

Bladder cancer is identified and resected during endoscopic examination of the bladder through the urethra. A new kind of photodynamic diagnosis (PDD) of bladder cancer (BC) was developed in 2001 where hexaminolevulinate or 5-aminolevulinic acid (5- ALA) is used as precursor to the dye. The aminoacid 5-ALA is metabolized to protoporphyrin IX (PPIX) in the malignant cells which fluoresces at approx. 635 nm when excited with blue light. However, a problem with this procedure is that yellow urine in the bladder is also excited by the blue light to generate strong green fluorescence. This confounds the fluorescence and the vision in the bladder becomes heavily impaired by the green fluorescence and thus the diagnosis of the malignant tissue.

By instead using excitation light with wavelengths greater than 500 nm and less than 550 nm, fluorescence from urine is avoided at the same time as enough autofluorescence from the bladder wall is obtained for the practitioner to obtain a clear view of the bladder wall and to further observe fluorescence from a photosensitive compound accumulated in precancerous, malignant and/or fast-growing cells in the bladder.

In one or more embodiments, the illumination system is for endoscopic applications in the bladder, where the LED light has an initial central wavelength between 500 and 550 nm.

The photosensitive compound used in that embodiment is preferably selected from the group of porphyrins, such as haematoporphyrin or protoporphyrin, preferably protoporphyrin IX (PPIX). The photosensitive compound is preferably delivered to malignant cells by means of a precursor based on levulinic acid, such as hexaminolevulinate (e.g. Hexvix(R)), 5-aminolevulinic acid (ALA or 5-ALA) or methyl aminolaevulinate (MAL, e.g. Metvix). Levulinic acid are metabolized to photosensitive PPIX in cells through the intrinsic cellular haem biosynthetic pathway.

The combination of the tuned monochromatic LED light 208 and the band rejection filter 224, preferably a narrow band notch filter, allows the surgeon to use the autofluorescence of the surrounding (healthy) tissue as normal examination light, because the irradiated tissue fluoresces and thereby becomes visible. In an example a 525 nm LED was used resulting in an autofluorescence spectrum from surrounding tissue of approx. 550-700 nm, i.e. only the green, yellow and red part of the visible spectrum, but still adequate for discerning the morphology of the tissue. Using the monochromatic light source generated autofluorescence light from the healthy tissue as normal examination light allows the surgeon to skip the use of bulky liquid core light guides and power consuming metal halide lamps or discharge lamps, like xenon lamps, normally used in many endoscopic procedures. Use of an LED as examination light source greatly reduces the footprint of the optical transmission path, because the light may be transmitted to the region of examination via a thin optical fiber with a diameter of 0.5 mm. And the power consumption of the excitation light source may also be reduced.

As the autofluorescence inside the bladder and other body cavities varies from patient to patient, tuning of the LED in the illumination system is highly advantageous, as the contrast between the different fluorescence colors can be optimized individually for each patient without changing filters or using expensive optics.

Figure 4B shows an image of the bladder before tuning the LED wavelength and 4C shows an image of the bladder after tuning the LED wavelength to obtain a maximum contrast signal for the viewer.

The system and the method of the present disclosure need only have one light source for illuminating the bladder, since the monochromatic LED generates sufficient autofluorescence in the bladder to allow an observer, e.g. a physician, to view the tissue irradiated by the light from the monochromatic LED because the irradiated tissue is being illuminated by the autofluorescence generated in the irradiated tissue, i.e. the tissue fluoresces whereby it becomes visible.

The possibility to perform photodynamic diagnosis of bladder cancer in the outpatient department combined with photo induced denaturation of tumour tissue inside the bladder of the patient greatly reduces the cost of bladder cancer / tumor diagnosis and treatment.

Endoscopic applications for diagnostic and treatment of bladder cancer

Bladder tumour disease is a disease normally experienced by elderly people with a median age of bladder tumours debut at 65 years. Less straining treatment is required, as populations and thus also patients get older and suffer from more comorbidity making them less fit for admittance to hospital and general anaesthesia.

Urothelial cancer of the bladder is the second most expensive cancer disease and the one of the most common cancer types detected in Europe. About 75% of the patients suffer from non-muscle invasive bladder cancer (NMIBC) and account for approximately 65% of the cost of bladder cancer treatment.

NMIBC is normally removed in general anesthesia either by admitting the patient for two-three days to a urology ward or in day-surgery settings. Generally, the prognosis of NMIBC is good, although 30–80% of cases will recur. In 1–45% of the cases NMIBC will progress to muscle invasion within 5 years. Consequently, NMIBC is a chronic disease with varying oncologic outcomes.

Traditionally, laser vaporization (LV) of bladder tumours to minimize surgical load or transurethral resection of bladder tumours (TUR-BT) has been tested for removing bladder tumours. Frequent recurrences requiring TUR-BT and lifelong surveillance account for the vast part of the treatment expenses, makes the cost per patient from diagnosis to death the highest of all cancer types.

Substantial health and patient resources can be spared if use of new technology can bring treatment of NMIBC from the inpatient to an outpatient office-based setup. Removal of small bladder tumours may be performed with diathermy in flexible cystoscopes under local anaesthesia. However, diathermy in local anaesthesia is only offered to a limited number of patients with small, usually solitary, recurrences. The limitation of diathermy is pain perception, resulting in reduced patient tolerance of the procedure.

The LV technique has traditionally been tested using either a Holmium laser emitting light with a wavelength of 2100 nm or a Thulium laser emitting light with a wavelength of 2013 nm to vaporize the entire tumour.

Removal of bladder tumours using the Holmium laser technique may produce less pain than diathermia. However, the method has mainly been used for patients unfit for general anesthesia, presenting solitary or few small tumours and without routine simultaneous biopsy. Also, when using this technique, the operation procedure normally takes between 15 to 35 minutes, which may be straining for a fragile elderly awaken patient.

Conventionally laser treatment methods focus on vaporization. Laser TUR-BT has mainly been tested in rigid cystoscopes and in the operating theatre in general anesthetic using Holmium or Thulium lasers to vaporize the entire tumour or using vaporizing to do én-bloc tumour resection. The experience is that the operation time may be longer for laser surgery than conventional TUR-BT, but the method is safe, excellent hemostasis is achieved, obturator nerve reflection is not seen and bladder perforation very rare. With regard to recurrence rates, laser based TUR-BT is more or less equal to TUR-BT using diathermia.

Lately, Thulium laser TUR-BT of non-invasive urothelial bladder tumours in selected patients was reported showing a recurrence rate at 14.5% during 16 months follow-up and a 2 year over all recurrence rate at 48% after Holmium laser TUR-BT. Similar results may be found after golden standard TUR-BT in general anaesthetic but data comparing laser TUR-BT and conventional TUR-BT are missing.

A system for photo induced denaturation of tumour tissue inside e.g. a bladder may be incorporated in a system comprising the illumination system. An example of such a system

400 is shown in figure 5. The illumination system 200 of figure 1 is shown in figure 5 in combination with a high intensity treatment light source 402 adapted for photo induced denaturation of tumour tissue inside the bladder in connection with treatment of bladder tumours.

The high intensity treatment light source 402 is in one or more embodiments a solid state light source emitting light 404 at a wavelength between 800-1000 nm. This wavelength range is in particularly suitable for photo induced denaturation of tumour tissue having a cauliflower shape as shown as item 102 in figure 4A.

Alternatively, the high intensity treatment light source 402 is in one or more embodiments a solid state light source emitting light at a wavelength between 350-500 nm. This wavelength range is in particularly suitable for photo induced denaturation of tumour tissue having a flat shape as shown as item 104 in figure 4A.

The high intensity treatment light source 402 emits light 404 and further comprises a second optical transmission path 406 for guiding light 404 from the high intensity treatment light source 402 to a distal end 228 of the endoscopic tube 226. The first optical transmission path 208 and the second transmission path 406 may be combined or two separate channels extending through the endoscopic tube 406.

In one or more embodiments, a third fibre is connected to or part of the high intensity treatment light source 402 the third fibre extending through the endoscopic tube when the cystoscope and the high intensity treatment light source are connected.

In one or more embodiments, the system 400 also comprises a cystoscope comprising an endoscopic tube 226 with a distal end 228 adapted for extending through a patient's urethra 106 into the patient's bladder cavity 100 and a second optical transmission path 406 for guiding light 404 from the high intensity treatment light source 402 to the distal end 228 of the endoscopic tube 226. The high intensity treatment light source 402 is adapted for photo induced denaturation of tumour tissue 102, 104 inside the bladder 100 of the patient.

The high intensity treatment light source 402 and the LED 202 are the only light sources in the system 400.

In one or more embodiments, the high intensity treatment light source 402 is a diode laser, a high power light emitting diode, or a fibre laser. Other laser types may also be imagined.

In one or more embodiments, the high intensity treatment light source 402 is a diode laser emitting light at a wavelength of 808 nm, 820 nm, 880 nm, 940 nm or 980 nm.

In one or more embodiments, the high intensity treatment light source 402 is a diode laser emitting light at a wavelength of 808 nm.

In one or more embodiments, the high intensity treatment light source 402 is a diode laser emitting light at a wavelength of 820 nm.

In one or more embodiments, the high intensity treatment light source 402 is a diode laser emitting light at a wavelength of 880 nm.

In one or more embodiments, the high intensity treatment light source 402 is a diode laser emitting light at a wavelength of 940 nm.

In one or more embodiments, the high intensity treatment light source 402 is a diode laser emitting light at a wavelength of 980 nm.

The conventionally used Holmium and Thulium lasers differs from the solid state light source used here as the high intensity treatment light source 402 in that the Holmium and Thulium lasers emit light at 2100 nm and 2013 nm, respectively, and not between 800-1000 nm or between 350-500 nm. At the infrared wavelengths of the Holmium and Thulium lasers, a strong optical absorption in water is present, which lead to a penetration depth of only 0.1 mm in water.

In the Holmium laser, being a pulsed laser, this leads to adiabatic heating of water and subsequent formation of steam bubbles, which ablate tissue mechanically but do not coagulate blood vessels. The continuous wave Thulium laser can coagulate blood vessels, but only if the fibre tip is in intimate contact with the blood vessel due to the strong absorbance of water at 2013 nm.

Thus, due to the very limited tissue penetration the Holmium and Thulium lasers, these laser cannot be used for de-vascularization as presented here.

An advantage of using a solid state light source in the form of e.g. a diode laser is the lack of steam bubble effect. Both the Holmium and the Thulium laser (however to less extent) creates steam bubbles, when their energy destructs the tissue which may affect visibility during the operation. Another advantages of solid state light sources in comparison with Holmium and Thulium lasers are a smaller box size and a much higher wall-plug efficiency i.e., how much of the main supply is converted into laser power and a lower price.

In this invention, photo induced denaturation / de-vascularization of the tumour by illuminating the blood vessels in the tumour base / root 108 with a wavelength between 800-1000 nm, which is absorbed in haemoglobin, results in a heating of haemoglobin. The accumulated heat in the haemoglobin and surrounding tissue cause clotting of the vessels and subsequent tumour ischemia. The tumour 102, 104 is not removed from the bladder 100 during the procedure, but exfoliates during the following days due to ischemia. Patients tell that they pass small tissue clots in the urine during days after treatment.

At one of the wavelength ranges used in this invention, i.e. 800-1000 nm, haemoglobin absorbs light efficiently, which results in an occluded vessels in the tumour base. At e.g. 980 nm the optical absorption coefficient in hemoglobin is 50 cm^{-1}, which is sufficient to heat and ensure coagulation of blood vessels in tumour. Furthermore, a low absorption coefficient of 0,3 cm^{-1} in water makes deep tissue penetration possible.

Shorter wavelengths absorbed more strongly by haemoglobin could also be used to treat carcinoma in situ of the bladder wall in order to prevent unintended heating of healthy tissue below which may cause pain.

Normally, wavelengths in blue spectral region are avoided for photocoagulation in medical treatments of the retina and skin diseases like telangiectasia and haemangioma. In the case of the retina it is to avoid absorption in xanthophyll (pigment of the macula). For treatment of skin diseases the blue light would be scattered too strongly (due to Rayleigh and Lorenz-Mie scattering).

The use of blue light for photocoagulation of blood vessels in tumour 102, 104 of the bladder may therefore be unique to the bladder. The high intensity treatment light source 402 may therefore emit light 404 at a wavelength of between 350-500 nm.

To limit stimulation of pain nerve fibres, a short pulse duration provided in intervals is normally used. The procedure most often provides basically no pain for the patient.

In one or more embodiments, the high intensity treatment light source 402 is a laser emitting a pulse with a duration of approximately 1 millisecond.

In one or more embodiments, the high intensity treatment light source 402 is a laser emitting a pulse in intervals of 1 milliseconds.

In one or more embodiments, the high intensity treatment light source 402 is a laser emitting a pulse with a duration of approximately 1 millisecond and in intervals of 1 milliseconds.

In one or more embodiments, the high intensity treatment light source 402 is a laser emitting pulses for an exposure treatment time of between 10-240 seconds, or between 10-120 seconds, or between 30-120 seconds, or between 30-60 seconds is used.

Normally, only the base 108 of the tumour 102, 104, and not the entire tumour is denaturized. A tumour up to a size of about 2 centimetres may be de-vascularize using a solid state light source between 800-1000 nm or 350-500 nm according to this invention. The de-vascularized tumour 102, 104 is left in the bladder 100 after treatment. As the tumour 102, 104 is left in situ but without blood supply, it will dye and fall off after some weeks. The tumour 102 ,104 then exfoliates due to ischemia.

Most suitable for removing cauliflower-shaped tumours 102 using photo denaturisation is a solid state light source between 800-1000 nm, whereas the flat tumours 104 are best removed used photo denaturisation with a solid state light source between 350-500 nm.

The procedure is almost pain free and do not include the use of pain killers. Normally, the patients can leave the outpatient department immediately after the cystoscope has been removed.

The high intensity treatment light source 402 is used in combination with a system comprising a cystoscope comprising an endoscopic tube 226 with a distal end 228 adapted for extending through a patient's urethra into the patient's bladder cavity, the endoscopic tube 406 being adapted to hold a first optical transmission path 410 for guiding light from the solid state light source, i.e. the high intensity treatment light source 226, to the distal end 228 of the endoscopic tube 226, and means for guiding the movement of the endoscopic tube when inserting the distal end of the endoscopic tube into the patient's bladder through the patient's urethra.

In one or more embodiments, the cystoscope is a flexible cystoscope.

In vitro experiments using a high intensity treatment light source in combination with the illumination system

An in vitro model was developed to achieve knowledge on dose and response relation between diode laser treatment and tissue destructive effect when combining the high intensity treatment light source with the tuneable LED light source. In this example, the high intensity treatment light source is a laser. The impact of varying laser illumination time, laser power and distance between fibre and target tissue were investigated.

To achieve knowledge on a dose/response relation between laser treatment time and tissue destructive effect, an in vitro model was developed where exact distance between the fibre from where the diode laser light emanates and the chicken breast meat lowered in the 37 Celsius degrees hot water. Water temperature was continuously monitored.

The laser treatment with a diode laser emitting light at 980 nm in 1 millisecond pulses at intervals of 1 millisecond was conducted for 10 seconds, 15 seconds, 30 seconds and 45 seconds. The 980 nm diode laser was set to an average power of 12 W. The diode laser was a 220 V / battery driven laser with a green 532 nm aiming beam and a front firing 400 µm 0,22 numerical aperture bare laser fibre attached (Fox Laser; dimensions: 14 x 16 x 17 cm and 1.2 kilo; A.R.C. Laser GmbH, Nüremberg. Germany).

The distance between the chicken meat and a fibre connected to the diode laser for controlling the illumination distance between the laser light and the chicken meat was set to 0 mm, the fibre just touching the meat without applying pressure to the chicken meat. Figure 6a shows the laser induced tissue destruction in chicken meat after 45 seconds of laser illumination.

Depth and width of tissue coagulation/vaporization was measured in 5 mm wide and 10 mm deep biopsies from the chicken breast meat. The biopsies were examined in a microscope and the depth and width of the tissue coagulation/vaporization was detected. A stereo-microscope (Olympus SZ61, Olympus, Tokyo, Japan; light source: Intralux® 4100, Volpi, Auburn, NY) was used. Bright field images were captured using a camera mounted to the microscope (ProgRes, CT3 USB, Jenoptik, Jena, Germany) and depth and width of tissue coagulation/vaporization was measured with associated software (ProgRes CapturePro v. 2.8.8, Jenoptik, Jena, Germany).

Measurements were done six times per period. Each experiment was done six times and results presented as median and quartiles. Pearson´s correlation coefficient, r, was calculated to evaluate correlation between duration of laser illumination time and magnitude of tissue destruction.

Figure 6b shows the tissue destruction depth as a function of the laser treatment time and figure 6c shows the tissue destruction width as a function of the laser treatment time. From figure 6b it can be seen that the destructive effect in depth appears to reach a maximal effect after between 30 to 45 seconds. Contrary, the width of the tissue destruction as shown in figure 6c seems to have a constant level between 2-3 millimetre.

Table 1 summarizes the results in figure 6b and 6c. Pearson´s r correlation coefficient for illumination time and depth of tissue destruction was 0.84 ($P<0.0001$) The destructive effect appears to reach a near maximum of 4.1 mm after 30 seconds of laser illumination after which the tissue destruction levels off. The width of tissue destruction appeared less related with illumination time being between 2-3 mm (Table 1; $r= 0.71$; $P<0.0001$).

Table 1. Relation between duration of laser illumination time and magnitude of tissue destruction.

Laser illumination time (seconds)	Depth of tissue destruction (µm, n=6 samples)			Width of tissue destruction (µm, n=6 samples)		
	Median	25% quartile	75% quartile	Median	25% quartile	75% quartile
10	2472	1847	2533	1987	1807	2091
15	2920	2575	3216	1861	1681	2091
30	4113	3922	4485	3080	2577	3366
45	4487	4225	4623	2807	2671	3138

To evaluate the influence of greater distance between laser fibre tip and target on tissue destructive effect, six tests were performed using 2 mm distance and laser illumination for 30 sec. These settings reduced the median depth of tissue destruction from 4.1 mm to 1.5 mm and the median width from 3.0 mm to 1.7 mm. The distance of 2 mm mimics the clinical situation when we treat bladder tumours.

The in vitro results of the depth of penetration of energy into chicken meet presented in figures 6b, is in accord with the absorption spectrum of prevailing body chromophores and related tissue penetration.

Measurements of tissue penetration to the side (see figure 6c), has to our knowledge not been presented before. Tissue penetration next to the laser fibre is important knowledge as treatment may involve laser activity having the fibre placed parallel and close to the adjacent bladder wall. Knowing that the laser do not harm adjacent tissue next to the fibre deeper than 2-3 mm and thus do not penetrate the bladder wall makes this procedure much safer than the conventional laser based treatment methods. It may even secure that tumour tissue below the mucosa is destroyed and thus exert a clinical effect.

In vivo experiments using a high intensity treatment light source in combination with the illumination system

In the in vivo experiments, a flexible cystoscope (Karl Storz) was used through which a 400 micron fibre was introduced into the bladder through the urethra.

Figure 7a-e show the inside of a bladder in a 62 years old male patient with a previous history of Ta low grade urothelial tumour at different time during treatment of bladder cancer. As can be seen in the before treatment picture in figure 7a, the patient has healthy tissue 700 and – before treatment – a 1.5 cm partly broad based tumour 702. Figure 7b is a picture taken during the treatment period and figure 7c is taken directly after the treatment has ended. In figure 7c, it can be seen that the tumour 700 is still attached to the healthy tissue 700.

The laser treatment procedure shown in figure 7a-c lasted two minutes and the entire procedure including a washing lasted for about 15 minutes. Afterwards, the patient could leave the OPO for returning to work.

The alternative standard treatment would require one to three days of hospitalization and surgery during general anaesthesia.

The diode laser in the in vivo studies was used with similar settings as for the in vitro studies. The tumour was given laser treatment for a total of two minutes at different places at tumour basis and the tumour was left in situ.

Biopsy and images of the tumour area shown in figure 7a-c was observed again 14 days and 4 months after treatment as shown in figure 7d and figure 7e, respectively. As can be seen in figure 7d no residual tumour was detected after 14 days – only a small reddening 704 of the treated tissue area is observable when comparing figure 7d and figure 7e.

During the entire laser treatment, saline was used to distend the bladder. No sedatives or pain treatment was given. The patient was awake and saw the treatment on a screen. Pain score was 0 on a visual log scale from 0-10 where 10 is maximal pain.

The complete disappearance of the tumour two weeks later end treatment (see figure 7d), was measured using photodynamic diagnosis (PDD; Hexvix; Photocure ASA, Oslo, Norway) guided cystoscopy performed in the operating theatre using a rigid cystoscope and having the patient in general anesthesia (Figure 7d). Biopsies from the tumour area comprised inflammatory tissue and no neoplasia.

Four months after the laser TUR-BT a PDD guided cystoscopy using a flexible cystoscope (PDD 11272 VPI, D-Light C Light source; Karl Storz, Tuttlingen, Germany) was performed in the OPD (see figure 7e). No recurrence but a scar was observed at the previous tumour place, and biopsy from the area comprised no dysplasia or tumour (Figure 7e).

Tumours all over the bladder may be treated using the setup described herein, even in the bladder neck when using a flexible cystoscope with endoscopic tubes in the form of smooth and bendable laser fibres.

The larger the tumour volume is, the more convenient is the de-vascularization method of this invention if the base can be addressed. The largest tumour size for treatment normally does not exceed 2-2.5 cm, but the number of tumours to be treated in one patient is less important. We have treated up to 10 tumours in a bladder of one patient may be treated during one treatment session.

To limit stimulation of pain nerve fibres, we used short pulse duration of 1 milliseconds with intervals of 1 milliseconds. This laser setting only gives minor pain and is for many patients painless. Pain score was in our patients between 0-3 on the visual analogue pain scale ranging from 0–10. Laser treatment on flat carcinoma in situ identified with PDD was more painful than treatment of exorphytic tumours. This phenomenon may be due to normal nerve supply in flat dysplastic mucosa in contrast to tumours.

References

100	bladder
102	cauliflower-shaped tumour
104	flat tumour
106	urethra
108	tumour base / root
200	illumination system
202	LED
204	light from the LED
205	optical bandpass filter
206	setup around the bandpass filter
208	first optical transmission path
210	tuned LED light
212	means for tilting the optical bandpass filter
213	first hybrid aspheric lens
214	second hybrid aspheric lens
215	third hybrid aspheric lens
216	additional filter
218	light emitted and/or reflected light from the endoscopic region of examination
220	optical collection path
222	an electronic imaging device
224	band-rejection filter
226	endoscopic tube
228	distal end of the endoscopic tube
400	system for photo induced denaturation of tumour tissue
402	high intensity treatment light source
404	light from the high intensity treatment light source
406	second optical transmission path
408	distal end of the endoscopic tube
700	healthy tissue
702	tumour
704	treated tissue area after the tumour has fallen off the bladder wall

Claims

1. An illumination system for fluorescence imaging applications such as endoscopic applications in a body cavity comprising bodily fluids or microscopic applications, the illumination system comprising:
   - a light emitting diode (LED) emitting substantially monochromatic LED light, wherein the LED is the single light source in the illumination system, and wherein the LED light emitted from the LED:
     - has an initial half width full maximum (FWHM),
     - has an initial central wavelength between 500 and 900 nm,
   - an optical bandpass filter adapted to reduce the initial FWHM, whereby LED light with a reduced FWHM is obtained;
   - means for tilting the optical bandpass filter thereby tuning the initial central wavelength of the LED light such that tuned LED light with a blue-shifted central wavelength is obtained;
   - an optical transmission path adapted to guide the tuned LED light to a region of interest being e.g. an endoscopic region of examination or a microscopic imaging plane;
   - an optical collection path adapted to guide light emitted and/or reflected light from the region of interest;
   - a band-rejection filter adapted to attenuate at least a part of the tuned LED wavelength for a viewer, and
   - an additional filter adapted for blocking light below 500 nm, the additional filter being positioned before or after the bandpass filter.

2. An illumination system according to claim 1, wherein the initial central wavelength is between 500 and 550 nm, or between 550 and 600 nm, or between 600 and 650 nm, or between 650 and 700 nm, or between 700 and 750 nm, or between 750 and 800 nm, or between 800 and 850 nm, or between 850 and 900 nm.

3. An illumination system according to any preceding claim, wherein the blue-shifted central wavelength is up to 50 nm lower than the initial central wavelength.

4. An illumination system according to any preceding claim, wherein the blue-shifted central wavelength is between 15-50 nm lower than the initial central wavelength.

5. An illumination system according to any preceding claim, wherein the optical bandpass filter is an interference filter.

6. An illumination system according to any preceding claim, wherein the additional filter is a cut-off filter.

7. An illumination system according to any preceding claim, wherein the illumination system further comprises a first hybrid aspheric lens and a second hybrid aspheric lens both positioned between the bandpass filter and the LED.

8. An illumination system according to any preceding claim, wherein the means for tilting the optical bandpass filter is a mechanical piezo or electronic adjustments means.

9. An illumination system according to any preceding claim, wherein the means for tilting the optical bandpass filter can tilt the optical bandpass filter around a first axis and/or a second axis, wherein both the first axis and the second axis extend through the middle of the bandpass filter along directions being perpendicular to the direction in which the LED light propagates, the second axis being perpendicular to the first axis.

10. An illumination system according to any preceding claim, wherein the optical transmission path and the optical collection path are fibres extending inside an endoscopic tube, the endoscopic tube having:
    - a proximal end where tuned LED light enters the optical transmission path, and light emitted and/or reflected light from the endoscopic region of examination exits by the optical collection path
    - a distal end where tuned LED light exits the optical transmission path and light emitted and/or reflected light from the endoscopic region of examination is collected by the optical collection path.

11. An illumination system according to any preceding claim, wherein a solid state imaging device is located at a distal end of the illumination system.

12. An illumination system according to claim 11, wherein the solid state imaging device is a CCD camera.

13. An illumination system according to claim 11, wherein the solid state imaging device is a CMOS camera.

14. An illumination system according to any preceding claim, wherein the band-rejection filter is adapted to attenuate the predefined wavelength by more than 10 dB, preferably by more than 20 dB, preferably by more than 30 dB, preferably by more than 40 dB, preferably by more than 50 dB, most preferably by more than 60 dB.

15. An endoscope comprising an illumination system according to any of the claims 1-14.

16. An endoscope according claim 15, wherein the endoscope is a digital endoscope.

17. An endoscope according claim 15 or 16, wherein a solid state imaging device, such as e.g. a CCD camera or a CMOS camera, is located at a distal end of the endoscope.

18. A method for tuning the wavelength of a light source for use in endoscopic photodynamic diagnostic in the cavity of a patient, the method comprising the steps of:
    - providing an illumination system according to any of the preceding claims, and
    - tilting the bandpass filter around a first and/or a second axis, thereby tuning the light from the LED towards shorter wavelengths, wherein both the first axis and the second axis extend through the middle of the bandpass filter along directions being perpendicular to the direction in which the LED light propagates, the second axis being perpendicular to the first axis.

19. A method according to claim 18, wherein the tilting of the bandpass filter done automatically based on an optimization for obtaining the most contrast in the fluorescence signal.

20. A system comprising:
    - an illumination system according to any of the claims 1-14, and
    - a high intensity treatment light source adapted for photo induced denaturation of tumour tissue inside the bladder in connection with treatment of bladder tumours,

    wherein the high intensity treatment light source is a solid state light source emitting light at a wavelength between 800-1000 nm or between 350-500 nm.

21. System according to claim 20, wherein the high intensity treatment light source is one of the following types:
    - a diode laser,
    - a diode laser emitting light at a wavelength of 808 nm,

- a diode laser emitting light at a wavelength of 820 nm,
- a diode laser emitting light at a wavelength of 880 nm,
- a diode laser emitting light at a wavelength of 940 nm,
- a diode laser emitting light at a wavelength of 980 nm,
- a high power light emitting diode, or
- a fibre laser.

22. System according to any of the claims 20-21, wherein the high intensity treatment light source emits a pulse with a duration of approximately 1 millisecond and with a duration of approximately 1 millisecond in intervals of 1 milliseconds.

23. System according to any of the claims 20-22 further comprising a flexible cystoscope.

24. System according to any of the claims 20-23, wherein the high intensity treatment light source is emitting pulses for an exposure treatment time of between 10-240 seconds, or between 10-120 seconds, or between 30-120 seconds, or between 30-60 seconds is used.

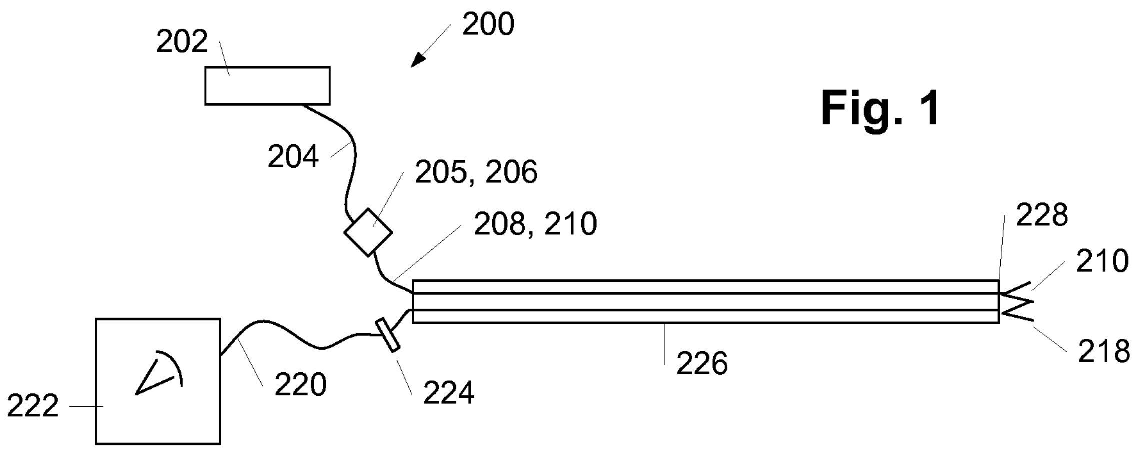


Fig. 1

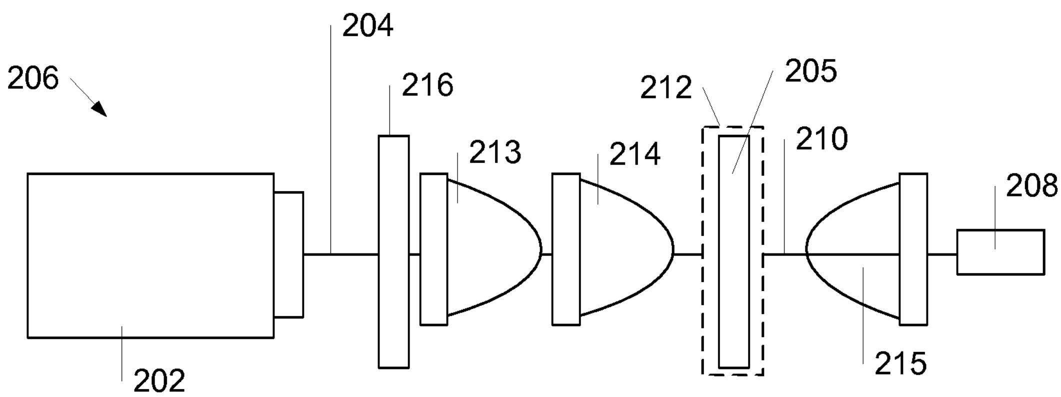


Fig. 2

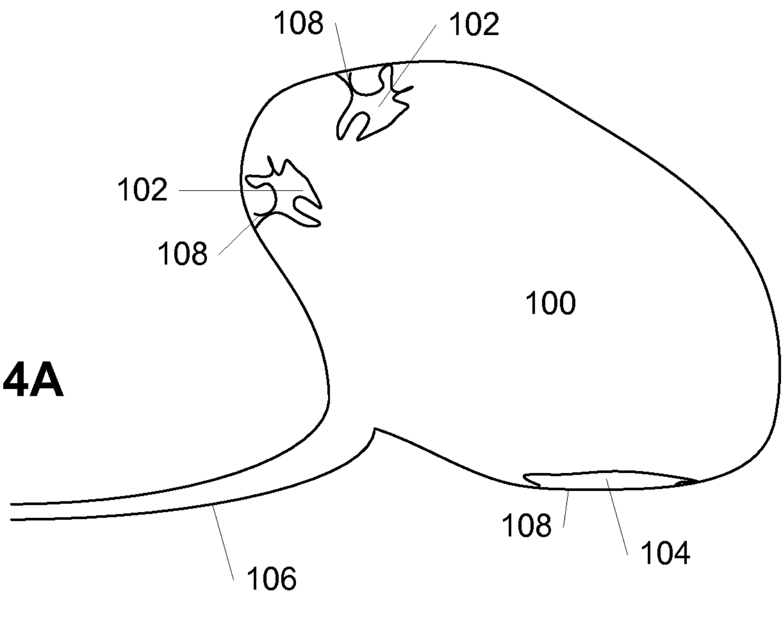


Fig. 4A

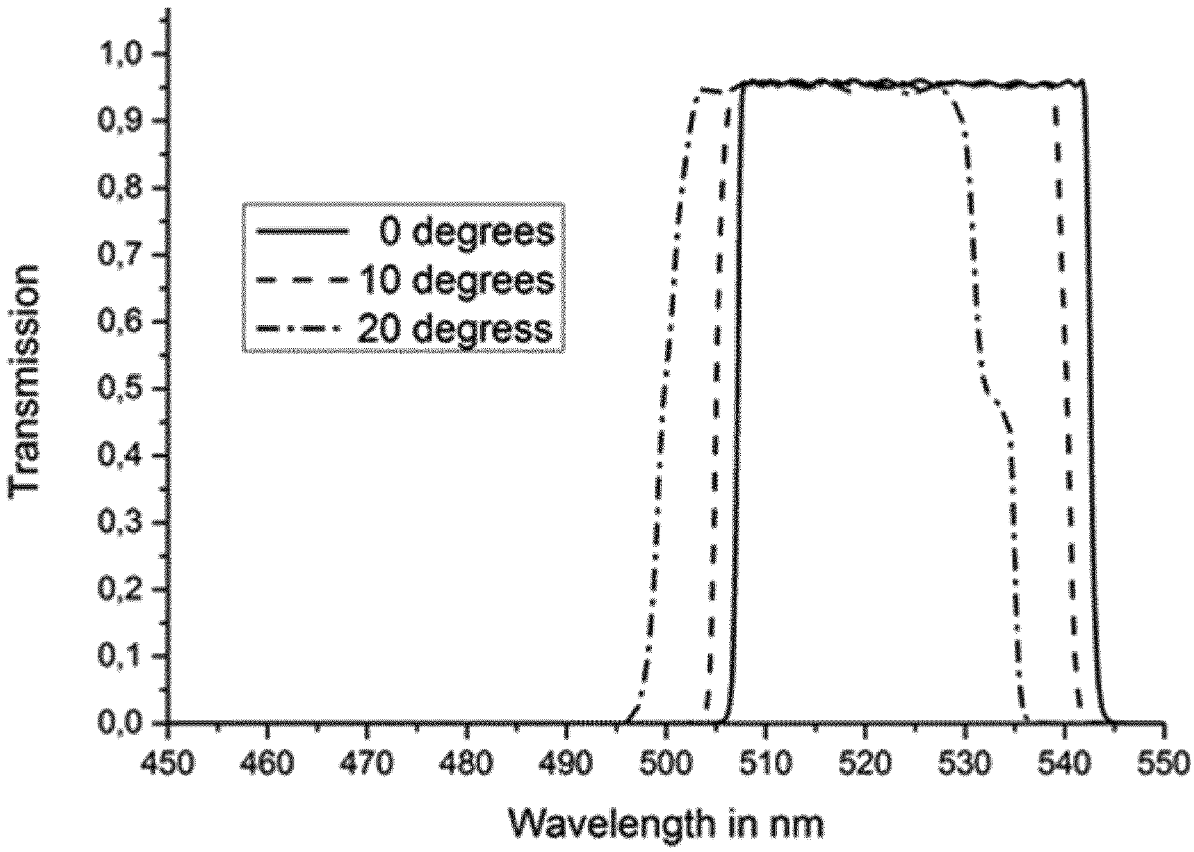

1,0
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0,0
Transmission
0 degrees
10 degrees
20 degress
450
460
470
480
490
500
510
520
530
540
550
Wavelength in nm

Fig. 3

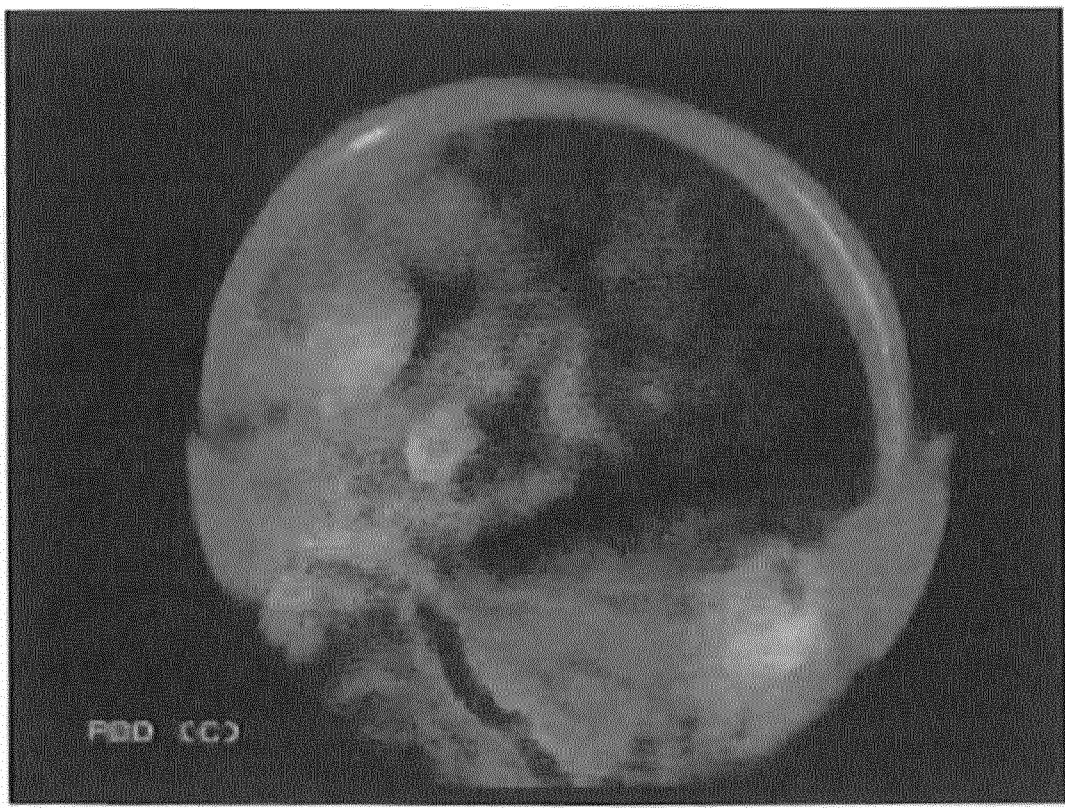


Fig. 4B

Fig. 4C

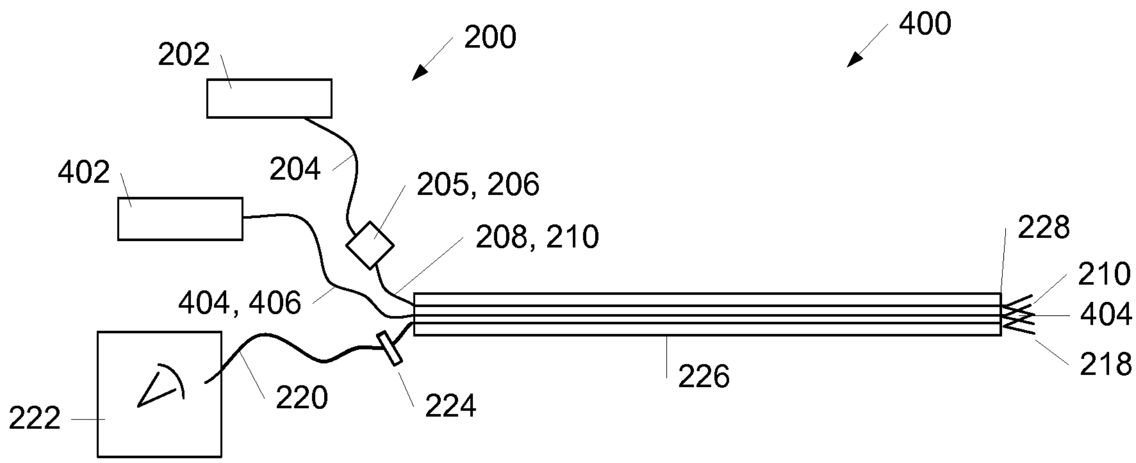

200
400
202
204
402
205, 206
208, 210
228
210
404, 406
404
218
226
222
220
224

Fig. 5

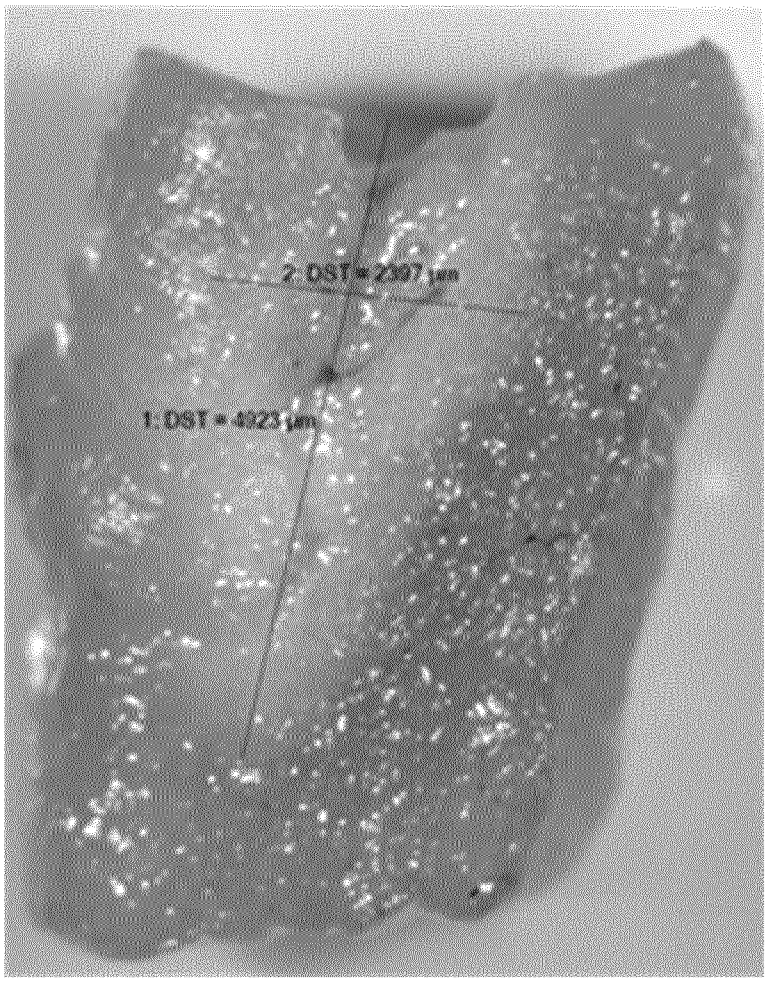

2: DST = 2397 µm
1: DST = 4923 µm

Fig. 6a

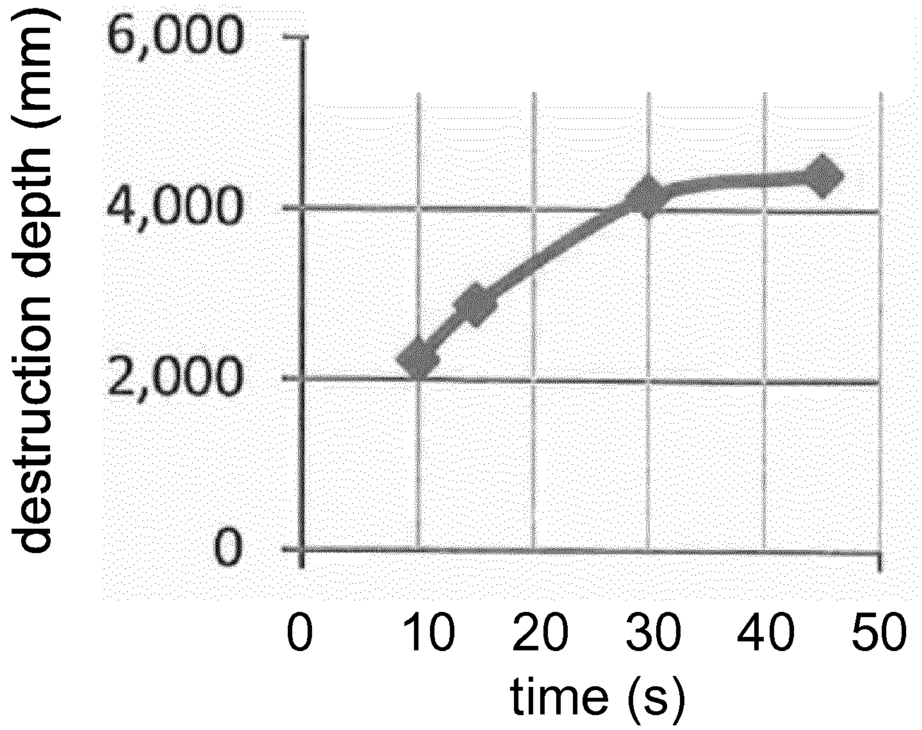
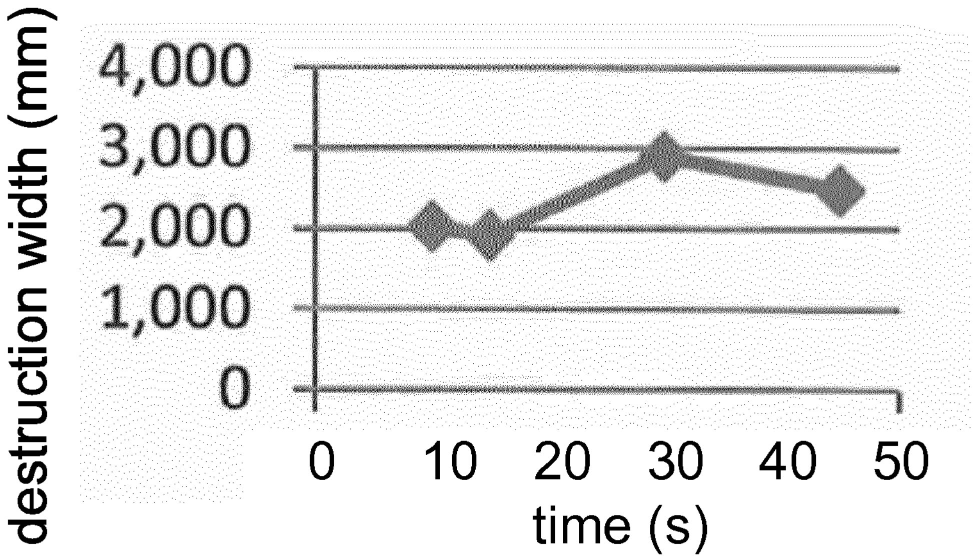

destruction depth (mm)
6,000
4,000
2,000
0
0
10
20
30
40
50
time (s)

Fig. 6b


destruction width (mm)
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3,000
2,000
1,000
0
0
10
20
30
40
50
time (s)

Fig. 6c

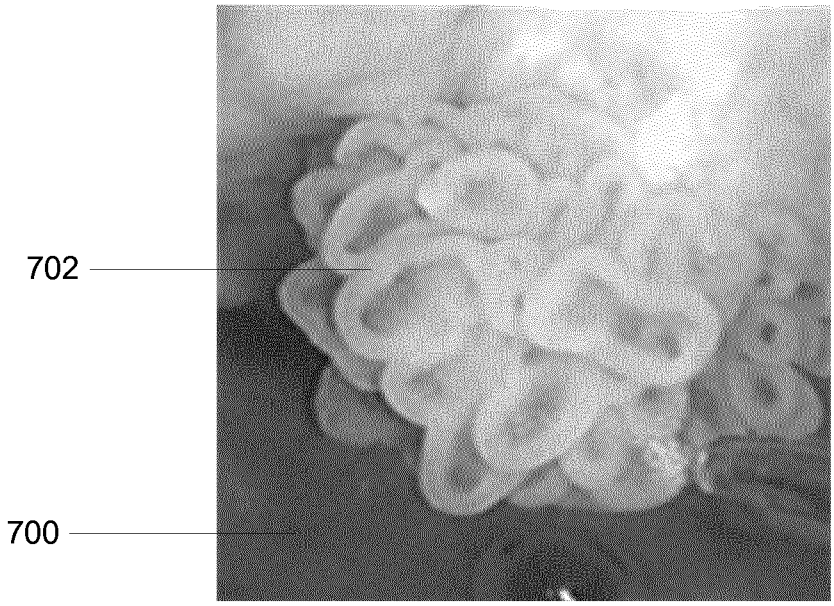

Fig. 7a

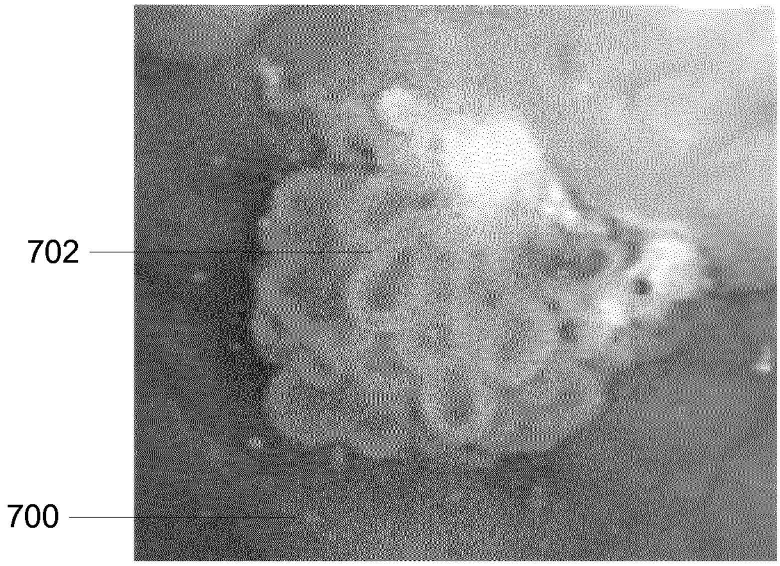

Fig. 7b

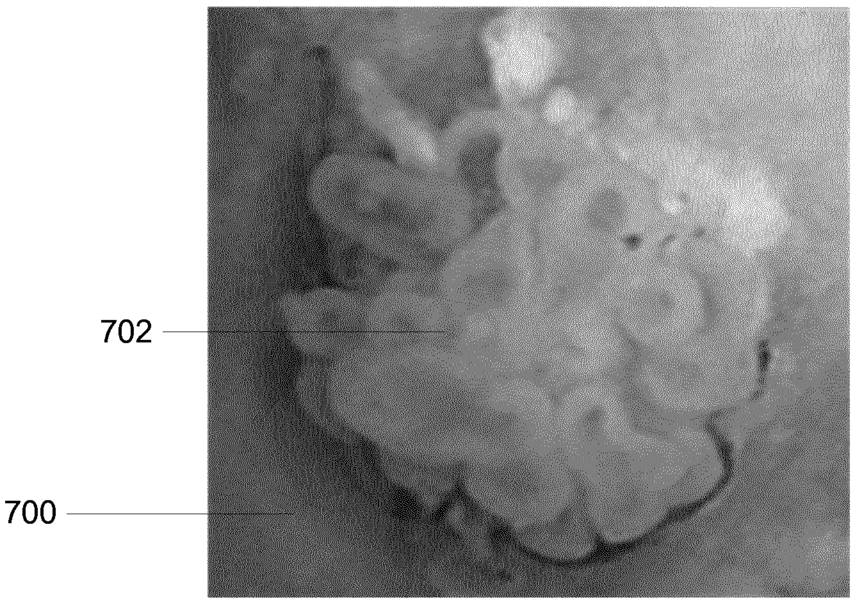

Fig. 7c

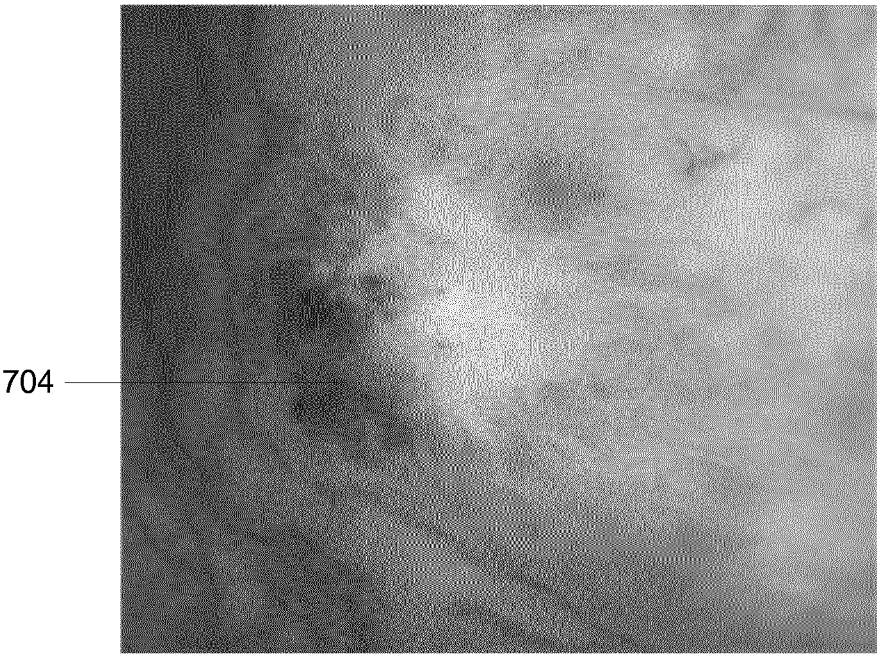

Fig. 7d

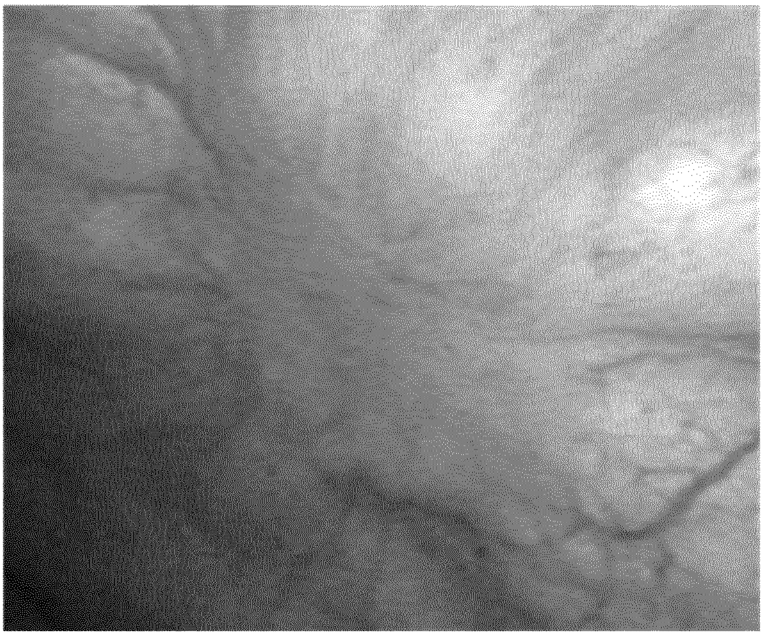

Fig. 7e

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/052531

A. CLASSIFICATION OF SUBJECT MATTER

INV.	A61B1/00	A61B1/04	A61B1/06	A61B1/07	A61B1/307
ADD.	A61B5/00	A61N5/06	F21V9/08	G02B5/28	G02B21/00
	G02B21/06	G02B23/24	G02B26/00	A61B18/24	

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B G02B G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LINDVOLD LARS R ET AL: "Method for improving photodynamic diagnosis and surgery of bladder tumours using cystoscopes", PROGRESS IN BIOMEDICAL OPTICS AND IMAGING, SPIE - INTERNATIONAL SOCIETY FOR OPTICAL ENGINEERING, BELLINGHAM, WA, US, vol. 9303, 26 February 2015 (2015-02-26), pages 93030V-93030V, XP060045926, ISSN: 1605-7422, DOI: 10.1117/12.2078780 ISBN: 978-1-5106-0027-0 sections 1, 2.2 to 2.4 figure 3 to 5 -/--	1-17, 20-24

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 March 2017	03/04/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Hemb, Björn

4

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	-& "525/30 nm BrightLine single-band bandpass filter", , 12 April 2016 (2016-04-12), XP055264658, Retrieved from the Internet: URL:https://www.semrock.com/FilterDetails.aspx?id=FF01-525/30-25 [retrieved on 2016-04-12] the whole document -----	
Y	JP 2 938881 B2 (NIDEK KK) 25 August 1999 (1999-08-25) abstract figure 4 -----	1-17, 20-24
Y	US 5 410 206 A (LUECKE FRANCIS S [US] ET AL) 25 April 1995 (1995-04-25) column 5, paragraphs 2, 4 column 3, paragraph bridging - column 4 figures 1, 2 -----	8,9
Y	US 2015/088001 A1 (LINDVOLD LARS [DK] ET AL) 26 March 2015 (2015-03-26) paragraph [0061] -----	14
A	GB 2 347 521 A (WINTER & IBE OLYMPUS [DE]) 6 September 2000 (2000-09-06) page 6, paragraph 1st figure 1 -----	1-17

4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2017/052531

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 18, 19
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 18, 19

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery. Claims 18 and 19 are directed to a method for use in endoscopic photodynamic diagnostic in the cavity of a patient. From the description it follows that this method is performed via an endoscopic tube which is inserted into the patient's bladder through the patient's urethra (see p. 5, l. 34 to 37 to 13; p. 13, l. 1 to 14) for the endoscopic photodynamic diagnosis in the cavity of a patient. This step constitutes an invasive step representing a substantial physical intervention on the body which requires professional medical expertise to be carried out and which entails a substantial health risk even when carried out with the required professional care. Thus, this step is a surgical step and thereby the nature of the whole method is rendered surgical. Consequently, the method of claims 18 and 19 is excluded from patentability according to Rule 39.1(iv). No written opinion will be drafted in respect to these claims (see Art. 17(2)(a) PCT, Rule 66.1(e) PCT).

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2017/052531

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 2938881 B2	25-08-1999	JP 2938881 B2 JP H02114402 A	25-08-1999 26-04-1990
US 5410206 A	25-04-1995	NONE	
US 2015088001 A1	26-03-2015	CN 104244804 A EP 2793679 A1 US 2015088001 A1 WO 2013092740 A1	24-12-2014 29-10-2014 26-03-2015 27-06-2013
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